ORIGINAL COMMUNICATIONS

CANCER CHEMOTHERAPY: PAST, PRESENT, AND FUTURE—PART I

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Cancer is of major concern today because of its high mortality. It is estimated that 66 million people in this country will eventually develop cancer; 1983 estimates were 855,000 new cases and 440,000 deaths from cancer.

Because of limitations of surgery and radiation therapy in effecting a cure for cancer, chemotherapy has become increasingly important. The developments in the chemical control of cancer in man are encouraging.

This two-part paper covers the historical milestones in the development of the chemical and hormonal control of cancer, present successes with the use of polychemotherapy, and the hopeful trends in research. Part II will be published in a future issue of this journal.

Cancer is of major concern today because of its high mortality and progressively increasing death toll. It ranks second as a cause of death among men and women of all ages in the United States. Among women between the ages of 30 and 54 years, cancer is the most frequent cause of death. Among children between birth and 14 years of age, cancer causes more deaths than any other disease. Fifty percent of these occur from birth to age 4. Only accidents take a greater toll.

Cancer occurs in every country of the world, in both sexes, and at every age. It strikes with increasing frequency with advancing age. It has been found in all species of animals and lower vertebrates. Melanomas in certain fish are well known, as are leukemia in fowl, lymphosarcoma in dogs, and breast and lung tumors in mice, rats, rabbits, and dogs.

It has been estimated that 66 million people in this country will eventually develop cancer, and that by the end of 1983 there would have been 855,000 new cases and 440,000 deaths from cancer. In the 1970s there were an estimated 3.5 million cancer deaths—6.5 million new cases and more than 10 million patients under medical care for cancer. Table 1 shows the estimated new cases and deaths for the major sites of cancer in 1983.[1]

When at the turn of the century the first annual mortality statistics were obtained from ten states and the District of Columbia, there was little hope for any cure for cancer patients. In 1900 deaths from cancer totaled 48,000. Current cancer trends indicate a marked increase in deaths from cancer of the lung and pancreas and malignant melanoma, and a decrease in deaths from cancer of the stomach and uterus. Table 2 shows the five-year cancer survival rates for selected sites.[2]

Only 25 to 30 percent of patients with neoplastic

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TABLE 1. ESTIMATED NEW CASES AND DEATHS FOR MAJOR SITES OF CANCER* (1983)

Site	No. of Cases	Deaths
Lung	135,000	117,000
Colon, rectum	126,000	58,000
Breast	115,000	38,000
Prostate	75,000	24,000
Uterus	55,000**	10,000
Urinary tract	57,000	19,000
Oral	27,000	9,200
Pancreas	25,000	23,000
Leukemia	24,000	16,000
Ovary	18,000	12,000
Skin***	17,000	7,000
Total	855,000	440,000

*Estimates are based on rates from National Cancer Institute SEER Program 1973-1979 (SEER—Surveillance, Epidemiology and End Results developed from 11 population-based registries)
**If carcinoma in situ included, 99,000
***Estimated new cases of non-melanoma skin cancer, approximately 400,000[1]

disease survive five years with currently available methods of surgery and radiation therapy. It has been estimated that if a thorough application of existing knowledge, namely early diagnosis and early therapy, were more widely employed, another 25 percent of these patients could be saved. Because of the limitations of surgery and radiation therapy in effecting a cure for cancer in a significant number of patients, chemotherapy is being widely explored.

HISTORY OF CHEMOTHERAPY

Chemotherapy, the "Cinderella" of cancer research, is, by definition, the treatment of cancer with chemical agents or drugs. The developments in the use of chemical agents against cancer in man are encouraging. Chemotherapy has survived several decades of severe criticism and has now attained respectability. Today there are tumors that can be cured with drugs, others in which marked improvement occurs with drugs, and a few where little benefit occurs. The significant progress in the control of different types of disseminated neoplasms with the use of chemotherapeutic agents over the past 37 years lends hope for further successes in the treatment of cancer with drugs. With the proper application of the knowledge available today, many patients with cancer can have longer, better, and more useful lives.

Cancer has occurred in man and beast since antiquity. It has been found in the bones of dinosaurs in the Mesozoic era, 70 to 220 million years ago; in other mammals in the Pleistocene epoch of the Cenozoic era, 10,000 to 1 million years ago; and in man, as evidenced by Peruvian and Egyptian mummies and bodies from the Etruscan tombs dating from some 2500 years BC.

Experiences with the therapy of cancer have been recorded from the time of Imhotep to the present. The earliest recorded treatment was cautery with a hot iron mentioned in the Edwin Smith papyrus, circa 3000 to 2500 BC, and thought to be the teachings of the first physician, Imhotep. In the epic of India, the Ramayana, circa 2500 years BC, are descriptions of tumors and their treatment with the knife and with arsenic paste. Later, approximately 1500 BC, the Ebers papyrus details the treatment of ulcerated tumors with arsenic paste. This paste became known as the "Egyptian Ointment" and its use persisted for centuries.[3] The earliest cure of cancer was noted around 525 BC by Herodotus, who recorded that Attosa, daughter of Cyrus and wife of Darius, was cured of cancer of the breast by Democedes. Hippocrates (born 460 years BC), who coined the words "cancer" and "carcinoma" in some relation to the astrological constellation between Leo, the lion, and Gemini, the twins, used cautery on cancer of the neck. Celsus (30 BC to 38 AD) used the knife to excise cancer of the breast.[4,5]

Ventures in the chemotherapy of cancer have been reported at different times through the years. A statement by Burrows[6] in 1767 reads as follows: "Although the physicians of all nations from the time of Hippocrates to the present have by numberless researches and experiments made trial of everything in nature from the most innocent drug to the most virulent poison, both in the mineral and vegetable kingdoms, yet the disease still baffles the power of physic." Among the older diverse agents used have been aconite, acids, alkalies, arsenic, belladonna, black salves, electricity, pipe clays, silver, violet leaves, and toads. If these agents acted, they did so as local caustics or escharotics. During the 1800s, arsenic was one of the most frequently employed agents in the treatment of human cancer.[6,7]

Important milestones in cancer treatment oc-

TABLE 2. FIVE-YEAR CANCER SURVIVAL RATES FOR SELECTED SITES* (%) (1981)

	Localized Disease	Regional Involvement	Distant Metastasis
Bladder	72	21	4
Breast	85	56	10
Colon, rectum	71	44	8
Larynx	79	37	15
Lung	33	11	1
Oral	67	30	14
Prostate	70	61	20
Uterus, cervix	78	45	10
Uterus, corpus	86	50	22

*National Cancer Institute, Biometry Branch. Survival rates adjusted for normal life expectancy.[2]

curring between the years 1865 and 1900 are of interest. The first report of a chemical agent that was effective when used systemically was in 1865 when Lissauer[8] described marked improvement in a patient with leukemia following the use of potassium arsenite, or Fowler's solution. In 1868 Busch[9] noted that attacks of erysipelas in patients with malignant tumors were sometimes associated with regressions in the size of tumors. In 1891, Coley[9] inactivated cultures of streptococci isolated from patients with erysipelas and used these mixed toxins to treat patients with carcinoma. Because of inconstant effects and toxicity, the use of the toxins was generally discontinued.[9] The successful surgical therapy of carcinoma began about 1880, when safe anesthesia and knowledge of antisepsis occurred. The roentgen ray was discovered by Wilhelm Conrad Roentgen in November 1895, and with the discovery of radium by Curie and Bequerel in 1896, radiation therapy came into use in the early 1900s.

HISTORY OF HORMONE USE IN CANCER THERAPY

Major developments in the effective hormonal control of cancer began in 1896 and continued during the 1900s.[9] The existence of a relationship between the ovarian hormones and carcinoma of the breast was first demonstrated by Beatson[9] in 1896 when he reported on two cases in which regressions occurred in the size of visible soft tissue lesions following oophorectomy. In 1900 Boyd[9] reported a series of 54 collected cases of breast cancer; 19 showed objective improvement following oophorectomy. In 1926 Lacassagne[9] of the Radium Institute in Paris, following studies on the pathogenesis of carcinoma of the breast, proved that cancers may be produced in animals receiving prolonged treatment with estrogens. These observations led to the suggestion that antagonism of estrogen by androgen might provide a significant therapeutic advance in the treatment of inoperable mammary cancer.

The first clinical reports of androgenic therapy providing beneficial effects in patients with metastatic or advanced breast cancer were by Loeser (1939, 1941) and Ulrich[9] (1939). Subsequent reports by others[9] confirmed that testosterone may produce regressions in patients with carcinoma of the breast in approximately 21.4 percent of the cases. Adair[9] popularized this method. Nobel Laureate Charles Huggins and his co-workers[9] in 1941 developed the use of androgen deprivation therapy for prostatic carcinoma with the successful application of castration in the treatment of carcinoma of the prostate. Androgen control therapy, consisting of bilateral orchiectomy, the administration of estrogens, or both, then became fairly standard practice.

In 1944 Haddow and his associates[9] at the Chester Beatty Institute in England were first to report on regressions of metastatic breast cancer following the use of estrogens. In this country subsequent reports by Nathanson, Herrmann, Adair, and Woodard confirmed the use of estrogens in

these patients.[9] The importance of steroid therapy in breast cancer led the American Medical Association to issue a series of reports on the effects of steroid therapy on advanced mammary cancer based on compiled pooled data from many investigators. In 1951 it was concluded that hormonal therapy is palliative only.[9] In 1954 it was concluded that 44 percent of patients obtained objective improvement with estrogen therapy with a mean duration of 14.5 months.[9] The final report in 1960 concluded that androgens produced objective remissions in 21.4 percent of cancer patients and estrogens produced remissions in 36.8 percent (38 percent in those beyond their eighth postmenopausal year).[9] Responsive patients had significantly longer survival rates with androgen or estrogen therapy than unresponsive patients. Estrogens are the hormones of choice in postmenopausal patients.[10,11] Response rates of breast cancer to conventional hormone therapy with estrogens, androgens, progestins, and corticosteroids; to the newer hormone therapies with antiestrogens, tamoxifen, nafoxidine, and clomiphene; to medical adrenalectomy with aminoglutethimide; and to ablative therapy, oophorectomy, adrenalectomy, and hypophysectomy are similar and generally range between 20 and 30 percent.

During the early 1900s a variety of interesting attempts at cancer therapy in man were reported.[9] Although rare cures and occasional improvement were noted, these investigational trials of mostly immunotherapy and organotherapy (Table 3) were generally ineffective.

TABLE 3. INTERESTING EARLY ATTEMPTS AT CANCER THERAPY[9]

1912	Coca, Dorrence, and Lebredo: Vaccination with sterilized human tumor
1914	Vaughan: Serum and leukocytes from rabbits or sheep injected with human tumors
1924	Matshushita: "Carcinolysin" from plant "Haisung"
1930	Coffee and Humber: Extract of suprarenal cortex from sheep
1933 to 1936	Blumenthal and Jacobs: JB-5 "Vallethin"—Extracts of liver, pancreas, duodenum and spleen, and "Aristotrop" —JB-5 plus extract of stomach
1933	Braunstein: "Splendothelan"—Spleen and other reticuloendothelial tissues from rabbits, goats, or calves
1941	Thompson: H-11—Biologic extract of urine purported to contain excreted parathyroid hormone (England)
1943	Bogomolets: Serum from horses immunized with human spleen and bone marrow from fresh human cadavers—Russia (American serum—REIS)

THE MODERN ERA OF CHEMOTHERAPY

The modern era of clinical chemotherapy began with the introduction of effective drugs in the mid- to late 1940s. In 1945 Woglom, director of the Cancer Institute at Columbia, said, "Some may not realize how difficult the problem of treatment really is—it is almost, not quite, but almost as hard as finding some agent that will dissolve away the left ear, say, yet leave the right ear unharmed—so slight is the difference between the cancer cell and its normal ancestor."[7]

New anticancer chemicals have been steadily developed, yet only approximately 100 of the available compounds have had adequate clinical study in this country. There have, however, been important new developments in the control of cancer in man with the use of the anticancer drugs, first when used singly, then in combinations, and finally with surgery and radiation therapy. There are more than 50 drugs in use today that have demonstrated substantial changes in the wide variety of human tumors. Among the total of 600,000 compounds tested in animal screening programs of the National Cancer Chemotherapy Service Center and private industry, approximately 6,000 compounds have been found to have antitumor properties. Since many are toxic and since the cost to develop each is approximately $500,000, few reach clinical trial.[12] Figure 1 shows the introduction of new drugs into the United States since 1948 in chronological order.[13]

Cancer chemotherapeutic agents of value today in the control of human cancer are grouped into ten categories according to their mode of action.

Alkylating Agents

The seven alkylating agents in use today are (1) nitrogen mustard (Mustargen); (2) the ethylenimines—triethylenemelamine (TEM) and triethylene-thiophosphoramide (thiotepa); (3) chlorambucil (Leukeran); (4) cyclophosphamide (Cytoxan); (5)

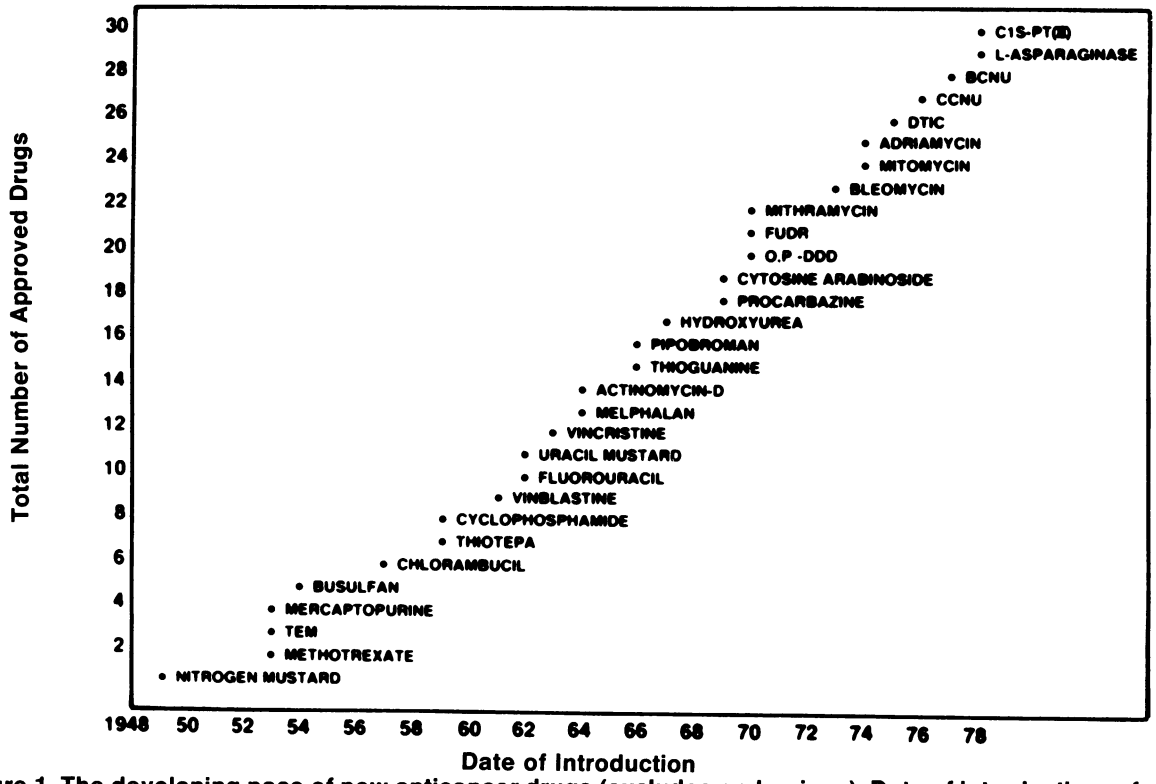

Figure 1. The developing pace of new anticancer drugs (excludes endocrines). Date of introduction refers to date of filing of new drug application with the Food and Drug Administration

melphalan (L-PAM); (6) busulfan (Myeleran); and (7) the nitrosoureas—carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU). The polyfunctional alkylating agents include a wide variety of chemical structures and are called radiomimetic agents because they act on the cell in the same fashion as does radiation. Tumor inhibition is by virtue of their cytotoxicity.

Mustard gas was discovered by Richie[9] in 1854 and prepared for manufacture by Meyer[9] in 1886. The nitrogen mustards were developed during World War I in the search for newer and better war gases. After the accidental sinking of a US naval vessel laden with mustard gas in the harbor of Bari, Italy, in 1942, it was noted that the poisoned sailors developed pancytopenia. Cornelius P. Rhoads, then chief of the Biological Branch of the US Army Chemical Warfare Service, initiated a large-scale screening program of hundreds of sulfa and nitrogen mustards. These agents were found to inhibit animal lymphoid tumors. In 1946, Gilman and Philips first observed and reported improvement in a patient with lymphosarcoma treated with tris-nitrogen mustard.[14]

The clinical effects of the alkylating agents are remarkably similar; however, a few apparent differences have been reported and this may account for the selection by some clinicians of a specific agent in the treatment of a certain type of tumor. Initial clinical trials with triethylenemelamine were reported by Rhoads et al,[15] Wright et al,[16] and Karnofsky et al[17]; with triethylenethiophosphoramide by Shay et al[18]; with chlorambucil by Haddow[19] and Galton et al[20]; with cyclophosphamide by Gross and Lambers[21,22] and Petrides[23]; with sarcolysin by Blokhin[24]; with melphalan by Holland and Regelson[25] and Papac et al[26]; with busulfan by Haddow and Timmis[27] and Galton[28]; and with carmustine by Ball et al.[29] In general these agents produce remissions of various degrees in lymphomas, Hodgkin's disease, chronic leukemias, breast cancer, ovarian cancer, lung cancer (especially oat-cell carcinoma), lymphoepithelioma of the nasopharynx, Kaposi's sarcoma, mul-

tiple myeloma, malignant melanoma, and neuroblastoma. They are also useful in the control of malignant effusions. With the use of triethylene phosphoramide, Farber et al[30] demonstrated a chemical action against the malignant melanoma for the first time in man. In the treatment of congenital retinoblastoma, Reese et al,[31] using a combination of irradiation plus triethylenemelamine, showed a significant improvement in the survival rate and in the prolongation of useful vision. Chlorambucil, an aromatic mustard, often produces remissions without the production of toxicity. Unlike the other alkylating agents, cyclophosphamide is also active against acute leukemias of children. Melphalan, when used with the regional perfusion technique, can cause complete regressions in malignant melanomas localized in an extremity.[32-34] Melphalan is widely used in patients with multiple myeloma and produces objective improvement in 58 percent of cases. Busulfan differs from the other agents because it has a specific depressant action against the production of myeloid cells without depressing lymphopoiesis; it is an agent of choice in the treatment of chronic myelogenous leukemia. The nitrosoureas are unusual because they are liposoluble and can cross the blood brain barrier, hence the current application in CNS tumors. Carmustine is used intravenously, the others orally.

Antimetabolites

An antimetabolite is a substance that competes with the action of a normally occurring essential metabolite in the body and usually has a chemical structure similar to that of that metabolite. There are three types of antimetabolites of clinical value—the folic acid antagonists, the purine antagonists, and the pyrimidine antagonists.

The folic acid antagonists developed by Subba Row and co-workers in 1947 were first shown in 1948 by Farber to produce remissions and an increase in the life span of children with acute leukemia.[35,36] In 1951 the author's group was first to demonstrate remissions in patients with breast cancer and other solid tumors using the chemical agent methotrexate.[37-39] This was the first time a chemotherapeutic agent was demonstrated to produce remissions in cancer of the breast. In 1960 the same group was first to produce striking remissions with methotrexate in patients with mycosis fungoides.[40,41] In 1956 Li et al[42] first demonstrated complete remissions in women with choriocarcinoma and chorioadenoma using methotrexate. Sullivan et al first achieved complete, and at times prolonged, tumor regressions in squamous cell carcinomas of the head, neck, and uterine cervix by the administration of large doses of methotrexate by continuous intra-arterial infusion.[9] These results are superior to the oral administration of the drug in these types of cases.[43] Methotrexate has been clearly established to have important antitumor effects in patients with leukemia, lymphomas, choriocarcinoma, breast cancer, squamous cell carcinomas of the head and neck, mycosis fungoids, and most recently with high-dose regimens in osteogenic sarcoma.

Of the purine antagonists developed by Hitchings and associates, 6-mercaptopurine is most important.[9] Its antileukemic activity was first demonstrated by Burchenal et al in 1953.[44] Its greatest usefulness is in producing remissions in childhood leukemia, but it is also effective against choriocarcinoma in women.

Azathioprine, which has antileukemic activity, is used primarily to suppress the immune response in kidney transplants and not for cancer therapy. Thioguanine is another drug effective in acute leukemia.

The pyrimidine antagonist fluorouracil was developed and synthesized by Heidelberger and Dushinsky, and its activity in cancer in man was shown by McIver et al[45] and Curreri et al.[46] Fluorouracil is of greatest importance in the temporary control of patients with adenocarcinomas of the gastrointestinal tract, including the stomach, colon, rectum, gallbladder, liver, and pancreas, and in the breast and some cancers of the female genital tract.[47]

A related pyrimidine antagonist in this group, 5-iodo-2′-deoxyuridine (IUDR), has therapeutic antitumor effects but is used primarily as a topical treatment of herpes simplex keratitis, a viral disease of the eye.[48]

Cytosine arabinoside, another compound in this group, is of great benefit and is now in widespread use in the treatment of acute myelogenous leukemia.[49] It was first demonstrated by Talley and Vaitkevicius[50] to be clinically active in lymphosarcoma and other tumors. Azacytidine is an agent useful in the treatment of refractory acute myelogenous leukemia.[51]

Antitumor Antibiotics

Antitumor antibiotics are substances isolated from soil micro-organisms. They are true antibiotics but are not employed in the treatment of bacterial diseases in man. They are used in the treatment of tumors and are an interesting group of compounds.

The first group of the antitumor antibiotics, the actinomycins, were isolated by Waxman and Woodruff in 1940.[43] Since then a number of actinomycins (eg, B, C, D, I, J, X, and P_2) have been discovered. Initial clinical trials with actinomycin C by Schulte in Germany in 1954 showed beneficial effects in a series of patients with neoplastic diseases involving the lymphatic system, particularly Hodgkin's disease.[43] Actinomycin C is widely used in Europe.[52-54] In this country, Farber et al[55] noted important useful effects of dactinomycin in children with rhabdomyosarcoma, Wilms' tumor and Hodgkin's disease. The most significant success with dactinomycin has been its sequential use in combination with surgery and radiation therapy in the treatment of Wilms' tumor.[56-58] Golomb et al[59] reported that three patients with malignant melanomas of the extremity showed total disappearance of the tumors following dactinomycin therapy administered by regional isolation perfusion.[10]

Mitomycin, an antibiotic isolated by Hata et al in 1956,[43] underwent extensive clinical testing in Japan, where it was found to be active against the chronic leukemias, lymphomas, and some epithelial tumors. In trials in this country it has been found active in a broad range of tumors including adenocarcinomas of the gastrointestinal tract, breast, and ovary; squamous cell carcinomas of the head, neck, and cervix; transitional cell carcinomas of the bladder; lymphomas; leukemias; and sarcomas.[60-63] As a single agent it is reported to be as effective against adenocarcinomas of the gastrointestinal tract as fluorouracil.

Mithramycin, a unique antibiotic, was initially demonstrated to have antitumor effects in man by Curreri and Ansfield in 1960.[64] As a single agent, mithramycin produced complete remissions in 10.8 percent and partial remissions in 26.2 percent of a large series of cases of embryonal carcinoma or choriocarcinoma of the testis, with the remissions lasting for an average of one year.[65,66] In the primary glioblastoma of the brain and in metastatic lesions to the brain, mithramycin produces important beneficial effects. Ransohoff et al reported on a series of these cases.[67] Since serum calcium levels are reduced by mithramycin, it is also employed effectively in the therapy of hypercalcemia in malignant and benign disease.[43]

Doxorubicin (Adriamycin), an anthracycline antibiotic isolated by Arcamone and DiMarco in 1969, was first demonstrated by Bonadonna et al and subsequently confirmed by many other investigators to have important effects on a broad spectrum of malignant tumors in man.[68] It works more effectively in a wider variety of tumors than any other drug in use today and is one of the more exciting current agents. Among the tumors in which striking remissions occur with its use are the lymphomas, the rare sarcomas (eg, synovioma and osteosarcoma), lymphoepithelioma, cancer of the thyroid, carcinoid tumors of the gastrointestinal tract, cancers of the breast, ovary, lung, intestinal tract, head and neck, penis, and testicle, and neuroblastoma.[69] The major limitation of doxorubicin is its dose-limiting cardiotoxicity. It is also a highly carcinogenic compound.

Bleomycin (Blenoxane), an antibiotic isolated by Umezawa in 1966, is active against squamous cell cancers of the head and neck, vulva, vagina, penis, scrotum, and various sites on the skin; the lymphomas; Hodgkin's disease; mycosis fungoides; and some testicular tumors. Its major limitation is the development of pulmonary fibrosis.[70,71]

Streptozotocin is an unusual antibiotic that, in addition to its antitumor activity, selectively depresses the function of the pancreatic beta cells (those producing insulin). Its clinical activity was first described by Murray-Lyon et al in 1968 in a case of islet cell carcinoma,[72] then confirmed by a National Cancer Institute study.[73] The major use of streptozotocin is in patients with islet cell carcinoma of the pancreas, in whom tumor regressions, amelioration of symptoms secondary to hormone secretions, and increases in survival times have occurred with its use. Other neuroendocrine, or APUD (amine precursor uptake and decarboxylation), tumors in which occasional moderate antitumor and antihormone effects have occurred with the use of streptozotocin are the carcinoid tumors of the gastrointestinal tract.[74] These are tumors associated with the carcinoid syndrome produced by secretions of serotonin, 5-hydroxytryptophane, kallikrein, histamine, ACTH, insulin, and prosta-

glandin, and with elevated levels of 5-hydroxyindoleacetic acid levels in the urine. Chlorozotocin, an analog of streptozotocin, is under study.

Daunomycin (Daunorubicin) is an antibiotic useful in acute leukemia, especially when used in combination with other drugs.

Streptonigrin (Bruneomycin) is another effective antitumor antibiotic with a broad spectrum of activity in the lymphomas and carcinomas. Its clinical activity was first described by Hackenthal et al[75] and Wilson et al.[76] The effectiveness of the oral administration of streptonigrin in the study of Harris et al was particularly noteworthy.[77]

Dihydro E73 (NSC-33012), an antibiotic with antitumor properties, was demonstrated by the author and colleagues[78] to produce striking and significant carcinolytic effects in patients with squamous cell carcinomas of the head and neck and vulva lasting for months, but these effects were noted only when the drug was administered by the isolation perfusion technique. Remissions in squamous cell lesions produced by dihydro E73 were as impressive as those produced by cisplatin, methotrexate, and some platinum combinations in the author's experience. Further study seems warranted with dihydro E73.

The next three major classes of anticancer compounds include the plant alkaloids, enzymes, and inorganic metal salts.

Plant Alkaloids

The first group of plant alkaloids are the vinca alkaloids. The vinca alkaloids are from the periwinkle plant, which has been used for many years in folk medicine in the treatment of diabetes, toothaches, hemorrhages, and wounds. These alkaloids are acute mitotic inhibitors that bind to microtubular protein involved in spindle formation in the metaphase. This mechanism of action differs vastly from that of the other cancer chemotherapeutic agents.

The general spectrum of antitumor activity of the vinca alkaloids is similar and includes the lymphomas, Hodgkin's disease, leukemia, breast carcinoma, ovarian carcinoma, choriocarcinoma and embryonal carcinoma of the testis.[79-86] Of clinical interest is the fact that these compounds can produce remissions in radiation-resistant tumors. The major distinguishing factor in these drugs is their toxicity. Vinblastine and vindesine display myelosuppression, whereas vincristine and vindesine produce neurotoxicity (eg, neuropathies, constipation).

The podophyllin derivatives are from the plant known as the May apple or wild mandrake podophyllin, extracts of which have been used for years as choleretic and cathartic agents as in Carter's Little Liver Pills, and locally in the control of superficial skin lesions and bladder papillomas. Like the vinca alkaloids, the podophyllin derivatives are mitotic inhibitors.

Etoposide VP16-213 and Teniposide VM26 have been widely used in Europe. Recent trials by the European Cooperative Group clearly demonstrated therapeutic effects in leukemia, Hodgkin's disease, lymphomas, testicular cancer, and ovarian cancer.[87,88] VP-16 is emerging as an impressive drug for the treatment of oat-cell or small-cell carcinoma of the lung, both as a single agent and in combination with other drugs where objective-response rates approach 44 percent. The VM-26 is better in the lymphomas and less active in lung cancer.[88,89] It has taken 30 years for a podophyllin derivative to become available for clinical use in the United States.

Enzymes

Asparaginase (Elspar) is found in animal tissues and bacteria. Its antilymphoma activity was discovered by Kidd in 1953.[90] This enzyme acts by decreasing the level of the amino acid asparagine. Some neoplastic cells, however, depend upon this amino acid for survival. It is clear that this is another compound that produces a state of remission in children with acute leukemia.[91-94] Because of limited supply, its spectrum of activity in other tumors in man is yet to be determined.

Inorganic Metal Salts

Cisplatin (Platinol) was introduced by Rosenberg in 1969.[95,96] When the effects of electrical currents on the replication of bacteria were studied, inhibition of the bacteria occurred and platinum complexes with antitumor activity were found in the broth. In 1971 Hill and associates[97] reported the first clinical activity of platinum. Cisplatin is the first of a new series of drugs with marked effectiveness in a broad spectrum of tumors that include squamous cell tumors of the head and neck, cervix, and esophagus; tumors of the uterus,

prostate, and bladder; osteogenic sarcoma; and neuroblastoma.[91,98,99] Its introduction has made a major difference in the control of squamous cell and testicular tumors. Like doxorubicin it is one of the new drugs in recent years that have made a major impact on the control of cancer in man.

The major limitation of cisplatin is its impairment of renal function. It causes degeneration of the proximal tubules, and to a lesser extent, ototoxicity, paresthesia, and other neurotoxicity.

Miscellaneous Compounds

The following compounds have produced therapeutic effects against certain types of tumors: mitotane, quinacrine, procarbazine, hydroxyurea, and dacarbazine.

Mitotane (Lysodren) is of special interest because it suppresses normal adrenal function in man. Bergenstal et al[100] demonstrated its beneficial effects in patients with metastatic adrenocortical cancer, a rare tumor that produces excess steroids resulting in Cushing's syndrome. Mitotane produces objective tumor regressions as well as steroid suppression in these cases.[101]

Quinacrine (Atabrine), one of the effective antimalarial compounds, was found by Gellhorn and associates[102] to control neoplastic effusion without the concomitant production of bone marrow depression when used locally intrapleurally or intraperitoneally.

Procarbazine (Matulane) is an important synthetic drug that was demonstrated to be useful in the treatment of Hodgkin's disease and the lymphomas by Mathé et al[103] in 1963. It has been found effective in providing remissions in patients whose tumors have become resistant to prior therapy with the alkylating agents and the vinca alkaloids. Its usefulness is limited because of the development of central nervous system symptoms (eg, psychosis, neuropathy).

Hydroxyurea (Hydrea), synthesized in 1896,[91] is a drug effective in the treatment of chronic myelogenous leukemia, but of limited use in the treatment of squamous cell lesions of the head and neck.[92-94] It warrants further investigation to delineate its full spectrum of activity.

Dacarbazine (DTIC-Dome), when given systemically, is the most effective drug available today in the production of temporary remissions in 20 percent of patients with disseminated malignant melanoma lasting for periods of four to seven months.[104] Activity with this drug has been noted in some sarcomas and Hodgkin's disease.[91]

Compounds Under Investigation

The drug of most interest in the group under investigation is interferon. The interferons, discovered in 1957 by Isaacs and Lindenmann,[105] are species-specific proteins produced by nearly all nucleated cells induced by viruses or other substances.[106] In turn, interferons have viral and cell multiplication inhibitory activities. Early clinical reports with leukocyte interferon indicate tumor regressions occur in patients with leukemia, lymphomas, multiple myeloma, breast cancer, Kaposi's sarcoma, and a few other tumor types.[107-111] Further trials are necessary before its place in the armamentarium of anticancer therapy can be determined. Interferon is of promise and unique in its source.

Retinoids are synthetic relatives of vitamin A that prevent the development of bladder tumors in animals. They are currently under study in bladder and skin tumors.[112-114]

Methyl Gag is a compound that was found active in producing remissions in adult acute myelogenous leukemia, lymphomas, and head and neck tumors in the early 1960s. Its use was discontinued because of toxicity. There is renewed interest in Methyl Gag because of a new, safer dose schedule.[91]

M-AMSA, an acridine derivative, is a DNA-binding drug that has had an effect in some leukemias and in breast cancer.[115,116]

Spirogermanium is a metal complex recently reported from Sweden in a phase II study to be effective in ovarian carcinoma, lymphomas, and a few other types of tumors.[117,118]

Ellipticinium, a plant alkaloid, is under study by the European Cooperative Group and has some activity in breast cancer.[119]

Norgamen (thioproline) is a compound under study in Spain in head and neck tumors.[120]

Razoxin (Razoxane) (ICRF-159) is under investigation in colorectal cancer.[91,121]

The anthracycline derivatives, compounds related to doxorubicin, are under investigation in the search for one with antitumor activity but with less cardiotoxicity than doxorubicin.[122] Mitoxantrone (Novantrone) is of most interest at present.

Part II of this article, which completes the discussion of "The Modern Era of Chemotherapy" and presents the author's views on future developments, will appear in a forthcoming issue of this journal.

Literature Cited

1. Cancer Facts and Figures 1983. American Cancer Society, 1982.
2. Cancer Facts and Figures 1981. American Cancer Society, 1980.
3. Slaughter DP. An introduction to cancer and cancer diagnosis. In: Field JB, ed. Cancer—Diagnosis and Treatment. Boston: Little, Brown, 1959, pp 1-11.
4. Pack GT, Ariel IM. A half century of effort to control cancer: An appraisal of the problem and an estimation of accomplishments. Collective Rev Surg Gynecol Obstet 1955; 100:59-161.
5. Pack GT, Ariel IM. The history of cancer therapy. In: Cancer Management: A Special Graduate Course on Cancer Sponsored by the American Cancer Society, Inc. Philadelphia: JB Lippincott, 1968, pp 2-27.
6. Haddow A. Note on chemotherapy of cancer. Br Med Bull 1947; 4:417-426.
7. Woglom WH. General review of cancer therapy. In: Mouton FR, ed. Approaches to Tumor Chemotherapy. Washington, DC: American Association for the Advancement of Science, 1947, pp 1-12.
8. Lissauer in Bendorf: II Zwei falle von Leucaemie, Mitgetheilt. Berl Klin Wochnschr 1865; 2(Oct):403-404.
9. Wright JC. Clinical cancer chemotherapy. NY State J Med 1961; 2:61:249-280.
10. Subcommittee on Steroids and Cancer of the Committee on Research, Council of Pharmacy and Chemistry, American Medical Association. Current status of hormone therapy of advanced mammary cancer. JAMA 1951; 146:471-477.
11. Subcommittee on Breast and Genital Cancer, Committee on Research, Council on Drugs, American Medical Association. Androgens and estrogens in the treatment of disseminated mammary carcinoma. Retrospective study of nine hundred forty-four patients. JAMA 1960; 172:1271-1283.
12. Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven, 1982, pp 1-15.
13. De Vita VT Jr. Principles of Chemotherapy. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1982, p 148.
14. Gilman A, Philips FS. The biological actions and therapeutic applications of the B-chlorethylamines and sulfides. Science 1946; 103:409-415.
15. Rhoads CP, Karnofsky DA, Burchenal JH, Craver LF. Triethylenemelamine in the treatment of Hodgkin's disease and allied neoplasms. Trans Assoc Am Physicians 1950; 63:136-146.
16. Wright LT, Wright JC, Prigot A, Weintraub S. Remissions caused by triethylenemelamine in certain neoplastic diseases. J Natl Med Assoc 1950; 42:243-251.
17. Karnofsky DA, Burchenal JH, Armstead GC Jr, et al. Triethylenemelamine in the treatment of neoplastic disease. AMA Arch Intern Med 1951; 87:477-516.
18. Shay H, Zarafonetis C, Smith N, et al. Treatment of leukemia with triethylene thiophosphoramide (thio-tepa): Preliminary results in experimental and clinical leukemia. AMA Arch Intern Med 1953; 92:628-645.
19. Haddow A. Experimental and clinical aspects of the action of various carboxylic acid derivatives in the aromatic nitrogen mustard series. In: Wolstenholme GEW, Cameron MP, eds. Ciba Foundation Symposium on Leukemia Research. Boston: Little, Brown, 1954, pp 196-204.
20. Galton DAG, Israels LG, Nabarro JDN, Till M. Clinical trials of p-(di-2-chlorethylamino)-phenylbutyric acid (CB1348) in malignant lymphoma. Br Med J 1955; 2:1172-1176.
21. Gross R, Lambers K. Vorlaufige Klinische Beobachtungen mit einem neven N. Lost Phosphamidester in der Tumortherapie. Naturwissenshaften 1958; 45:66.
22. Gross R. Clinical studies with B-518. Symposium Scientific Division. Brackwede, Germany: Asta-Werke AG, 1957.
23. Petrides P. Clinical experiments with B518. Symposium Scientific Division. Brackwede, Germany: Asta-Werke AG, 1957.
24. Blokhin NN. Theses and reports of the tenth session of the General Meeting of the Academy of Medical Sciences of the USSR. Moscow, 1956, p 61.
25. Holland JF, Regelson W. Studies of phenylalanine mustard (CB3025) in melastalic malignant melanoma of man. Ann NY Acad Sc 1958; 68:1122-1125.
26. Papac R, Galton DAG, Till M, Wiltshaw E. Preliminary clinical trial of p-di-2-chlorethylamino-L-phenylalanine (CB 3025, Melphalan) and of di-2-chlorethyl methane sulfonate (CB 1506). Ann NY Acad Sci 1958; 68: 1126-1127.
27. Haddow A, Timmis GM. Myeleran in chronic myeloid leukemia: Chemical constitution and biological action. Lancet 1953; 1:207-208.
28. Galton DAG. Myeleran in chronic myeloid leukemia. Br Med J 1953; 1:425-430.
29. Ball DP, Ben J, McCarthy DM. 1,3-bis(2chlorethyl)-1-nitrosourea (BCNU): Toxicity and initial clinical trial. Proc Am Assoc Cancer Res 1963; 4:55.
30. Farber S, Appleton R, Downing V, et al. Clinical studies on the carcinolytic action of triethylene phosphoramides. Cancer 1953; 6:135-141.
31. Reese AB, Hyman GA, Merriam GRJ, et al. Treatment for retinoblastoma by radiation and triethylene melamine. AMA Arch Ophthalmol 1955; 53:505-513.
32. Creech O Jr, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of cancer: Regional perfusion utilizing an extracorporeal circuit. Ann Sur 1958; 148:616-632.
33. Stehlin JS Jr, Clark RL Jr, Smith JL Jr, White EC. Malignant melanoma of the extremities: Experiences with conventional therapy; a new surgical and chemotherapeutic approach with regional perfusion. Cancer 1960; 13: 55-66.
34. Stehlin JS Jr, Clark RL Jr, White EC, et al. Regional chemotherapy for cancer: Experiences with 116 perfusions. Ann Surg 1960; 151:605-619.
35. Farber S, Diamond LK, Mercer RD, et al. Temporary remission in acute leukemia in children produced by folic acid antagonist, 4-aminopteroylglutamic acid (aminopterin). N Engl J Med 1948; 238:787-793.
36. Farber S. Some observations on the effect of folic

acid antagonists on acute leukemia and other forms of incurable cancer. Blood 1949; 4:160-167.

37. Wright JC, Prigot A, Wright BP, et al. An evaluation of folic acid antagonists in adults with neoplastic diseases. A study of 93 patients with incurable neoplasms. J Natl Med Assoc 1951; 43:211-240.

38. Wright JC. Proceedings of the second conference on folic acid antagonists in the treatment of leukemia. Blood (suppl) 1952; 7:178-181.

39. Wright JC, Cobb JP, Golomb FM, et al. Chemotherapy of dissiminated carcinoma of the breast. Ann Surg 1959; 150:221-240.

40. Wright JC, Gumport SL, Golomb FM. Remissions produced with the use of methotrexate in patients with mycosis fungoides. Cancer Chemother Rep 1960; 9:11-20.

41. Wright JC, Lyons M, Walker DG, et al. Observations on the use of cancer chemotherapeutic agents in patients with mycosis fungoides. Cancer 1964; 17:1045-1062.

42. Li MC, Hertz R, Spencer DB. Effect of methotrexate upon choriocarcinoma. Proc Soc Exp Biol Med 1956; 93: 361-366.

43. Wright JC, Medrek TJ, Walker DG, Lyons MM. The current status of chemotherapy and hormone therapy for cancer. In: Ariel IM, ed. Progress in Clinical Cancer, vol I. New York: Grune & Stratton, 1965, pp 264-307.

44. Burchenal JH, Murphy ML, Ellison RR, et al. Clinical evaluation of a new antimetabolite, 6 mercaptopurine in the treatment of leukemia and allied diseases. Blood 1953; 8:965-999.

45. McIver FA, Curreri AR, Meyer OO, et al. Clinical studies with 5-fluorouracil. Proc Am A Cancer Res 1957; 2:230.

46. Curreri AR, Ansfield FJ, McIver FA, et al. Clinical studies with 5-fluorouracil. Cancer Res 1958; 18:478-484.

47. Heidelberger C, Ansfield FJ. Experimental and clinical use of fluorinated pyrimidiner in cancer chemotherapy. Cancer Res 1963; 23:1226-1243.

48. Kaufman HE. Clinical cure of herpes simplex keratitis by 5-iodo-2' deoxyuridine (IDU). Proc Soc Exp Biol Med 1962; 109:251.

49. Bodey GP, Freireich EJ, Monto RW, Hewlett JS. Cytosine arabinoside therapy for acute leukemia in adults. Cancer Chemother Rep 1969; 53:59.

50. Talley RW, Vaitkevicius VK. Megaloblastosis produced by a cytosine antagonist 1-B-D-arabinofuranosyl cytosine. Blood 1963; 21:352-362.

51. Von Hoff DD, Slavik M, Muggia FM. 5-Azacytidine: A new anticancer drug with effectiveness in acute myelogenous leukemia. Ann Intern Med 1976; 85:237-245.

52. Schulte G. Erfahrungen mit neven cytostatischen mitteln bei Hamoblastosen und Carcinomen und die abgrenzug ihrer wirkungen gegen Rontgentherapie. Z Krebsforsch 1952; 58:500-503.

53. Schulte G, Lings H. Erfahrungen mit neven zytostatischen mitteln bei Leukosen und Lymphogranulomatosen und die abgrenzung ihrer wirkungen gegen Rontgentherapie. Strahlentherapie 1953; 90:301-306.

54. Schulte G. Resultados ulteriores en los pacientes con linfogrunolomatosis tratados con sanamicina (Actinomycin C "Bayer"). J Med 1954; 9:144-145.

55. Farber S, Maddock D, Swaffield M. Studies on the carcinolytic and other biological activity of actinomycin D. Proc Am Assoc Cancer Res 1956; 2:104.

56. D'Angio GJ, Farber S, Maddock S. Potentiation of x-ray effects by actinomycin D. Radiology 1959; 73:175-177.

57. Farber S. Chemotherapy in the treatment of leukemia and Wilms' tumor. JAMA 1966; 198:826-836.

58. Waksman SA, ed. The actinomycins and their importance in the treatment of tumors in animals and man. Ann NY Acad Sci 1960; 89:283-482.

59. Golomb FM, Postel AH, Gumport SL, Wright JC. Treatment of human malignant melanoma with actinomycin D. Proc Am Assoc Cancer Res 1963; 4:24.

60. Shimada N, Ishii R, Sato Y, et al. Experimental and clinical studies on mitomycins A and X. Chemotherapy 1956; 4:305-306.

61. Sukie K, Takeishi T, Noguchi T. Clinical trials of mitomycin C (antitumor substance). Chemotherapy 1957; 5: 223-224.

62. Mitomycin C. A preliminary report of studies of human pharmacology and initial therapeutic trial. Cancer Chemotherapy Rep 1959; 2:3-7.

63. Moore GE, Bross IDJ, Ausman R, et al. Eastern clinical drug evaluation program. Effects of mitomycin C (NSC-26980) in 346 patients with advanced cancer. Cancer Chemotherapy Rep 1968; 52:641-653.

64. Curreri AR, Ansfield FJ. Mithramycin—Human toxicology and preliminary therapeutic investigations. Cancer Chemotherapy Rep 1960; 8:18-20.

65. Kofman S, Eisenstein R. Mithramycin in the treatment of disseminated cancer. Cancer Chemotherapy Rep 1963; 32:77-96.

66. Kofman S. Mithramycin, an antibiotic used in cancer chemotherapy. Proc Am Assoc Cancer Res 1964; 5:36.

67. Ransohoff J, Martin BF, Medrek TH, et al. Preliminary clinical study of mithramycin (NSC-24559) in primary tumors of the central nervous system. Cancer Chemotherapy Rep 1965; 49:51-57.

68. Bonadonna G, Monfardini S, DeLena M, Fossati-Bellani F. Clinical evaluation of Adriamycin, a new antitumor antibiotic. Br Med J 1969; 3:503-506.

69. Young RC, Ozols RF, Myers CE. The anthracycline antineoplastic drugs. Medical Progress. N Engl J Med 1981; 16(3):305:139-153.

70. Clinical screening co-operative group of the European organization for research on the treatment of cancer: Study of the clinical efficiency of bleomycin in human cancer. Br Med J 1970; 2:643-645.

71. Crooke ST, Bradner WT. Bleomycin, a review. J Med 1976; 7:333-427.

72. Murray-Lyon IM, Eddleston ALWF, Williams R, et al. Treatment of multiple-hormone producing malignant islet-cell tumor with streptozotocin. Lancet 1968; 2:895-898.

73. Broder LE, Carter SK. Pancreatic islet cell carcinoma: Results of therapy with streptozotocin in 52 patients. Ann Intern Med 1973; 79:109-118.

74. Moertel CG. Clinical management of advanced gastrointestinal cancer. Cancer 1975; 36:675-682.

75. Hackenthal CA, Golbey RB, Tan CT, et al. Clinical observations on the effects of streptonigrin in patients with neoplastic disease. Antibiot Chemother 1961; 11:178-183.

76. Wilson WL, Labra C, Barrist E. Preliminary observations on use of streptonigrin as an anti-tumor agent in human beings. Antibiot Chemother 1961; 11:147-150.

77. Harris MN, Medrek T, Golomb FM, et al. Chemotherapy with streptonigrin in advanced cancer. 1965; 18: 49-57.

78. Wright JC, Gumport SL, Golomb FM. Dihydro E-73: A drug with anti-tumor effects in man. Preliminary clinical report. Cancer Chemother Rep 1960; 8:7-17.

79. Hodes ME, Rohm RJ, Bond WH. Preliminary studies on the therapy of acute leukemia with vincaleukoblastine. Proc Am Assoc Cancer Res 1960; 3:120.

80. Frei E III, Franzino A, Shnider B, et al. Clinical studies of vinblastin. Cancer Chemother Rep 1961; 12:125-129.

81. Armstrong JG, Dyke RW, Fouts PJ, Gahimer JE. Hodgkin's disease and carcinoma of the breast and other tumors treated with vinblastine sulfate. Cancer Chemother Rep 1962; 18:49-71.

82. Warwick OH, Alison RE, Darte JMM. Clinical experience with vinblastine sulfate. Can Med Assoc J 1961; 85: 579-583.

83. Dyke RW, Nelson RL. Phase I anti-cancer agents. Vindesine (desacetyl vinblastine amide sulfate). Cancer Treat Rev 1977; 4:135.

84. Dyke RW, Nelson RL. Initial clinical experience with vindesine (desacetyl vinblastine amide sulfate). In: Wicks CJ, ed. The Vinca Alkaloids Centennial Year Symposium. Basingstoke, Hants, England: Eli Lilly & Company, 1976.

85. Bodey GP, Freireich EJ. Initial clinical studies of vindesine (desacetyl vinblastine amide sulfate). Proc Am Assoc Cancer Res and Am Soc Clin Oncology 1976; 17:128.

86. Gralla RJ. Chemotherapy in lung cancer. In: Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven, 1982, pp 269-287.

87. Nissen NI, Larsen V, Pedersen H, et al. Phase I clinical trial of a new anti-tumor agent, 4-dimethylepipodophyllotoxin 9-(4,6-0-ethylidene-B-D-glucopyranoside) (NSC-141540-VP-16-213). Cancer Chemotherapy Rep 1972; 56: 769-777.

88. Brunner KW. European experience with VP 16-213. Presented at the Chemotherapy Foundation Symposium III. New Developments and Changing Concepts in Cancer Chemotherapy, New York, Oct 27-28, 1978.

89. Issell BF, Crooke ST. Phase I toxicity dose study etoposide (VP-16-213). Cancer Treat Rev 1979; 6:107-124.

90. Kidd J. Regression of transplanted lymphomas induced in vivo by means of normal guinea pig serum. 1. Course of transplanted cancers of various kinds in mice and rats given guinea pig serum, horse serum or rat serum. J Exp Med 1953; 98:565.

91. Dresler WFC, Stein R. Uber den hydroxylharnstoff (on hydroxylurea). Ann Chem Pharm 1869; 150:242-252.

92. Ariel IM. Therapeutic effects of hydroxylurea: Experience with 118 patients with inoperable solid tumors. Cancer 1970; 25:705-714.

93. Carter SK, Bakowski MT, Hellmann K. Chemotherapy of Cancer, ed 2. New York: John Wiley & Sons, 1981.

94. Kennedy BJ, Yarbro JW. Metabolic and therapeutic effects of hydroxyurea in chronic myelogenous leukemia. Trans Assoc Am Physicians 1965; 78:391-399.

95. Rosenberg B, VanCamp L, Krigas T. Inhibition of cell division in Escherichia coli by electrolysis products from a platinum electrode. Nature 1965; 205:698-699.

96. Rosenberg B, VanCamp L, Trosko JE, et al. Platinum compounds: A new class of potent anti-tumor agents. Nature 1969; 222:385-387.

97. Hill JM, Speer RJ, Loeb E, et al. Clinical experience with cis-platinous diammine dichloride (PDD). In: Hejzlar M, Semonsky M, Masak S, eds. Advances in Antimicrobial and Antineoplastic Chemotherapy. Baltimore: University Park Press, 1972, pp 255-257.

98. De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice. Philadelphia: JB Lippincott, 1982.

99. Prestayko AW, D'Aoust JC, Issell BF, Crooke ST. Cisplatin (cisdiaminedichloroplatinum II). Cancer Treat Rev 1979; 6:17-39.

100. Bergenstal DM, Hertz R, Lipset MB, Moy RH. Chemotherapy of adrenocortical cancer with o,p DDD. Ann Intern Med 1960; 53:672-682.

101. Heether AM Jr, Kayhoe DI. Adrenal cortical carcinoma. Results of treatment with o,p DDD in 138 patients. Am J Med 1966; 41:581.

102. Gellhorn A, Zaidenweber J, Ultmann J, Hirschberg E. The use of Atabrine (quinacrine) in the control of recurrent neoplastic effusions: A preliminary report. Dis Chest 1961; 39:165-176.

103. Mathé G, Schweisguth O, Schneider M, et al. Methylhydrazine in treatment of Hodgkin's disease and various forms of haematosarcoma and leukemia. Lancet 1963; 2:1077-1080.

104. Johnson RO, Metter G, Wilson W, et al. Phase I evaluation of DTIC (NSC 45388) and other studies in malignant melanoma in the central oncology group. Cancer Treat Rep 1976; 60:183-187.

105. Isaacs A, Lindenman J. Virus interference: I. The interferon. Proc R Soc Lond [Biol] 1957; 147: 258-267.

106. Lindenmann J, Burke DC, Isaacs A. Studies on production, mode of action and properties of interferon. Br J Exp Pathol 1957; 38:551-562.

107. Strander H. Interferons: Antineoplastic drugs, in press.

108. Strander H. Anti-tumor effects of interferon and its possible use as an antineoplastic agent in man. Tex Rep Biol Med, in press.

109. Baron S, Dianzani F, eds. The interferon system: A current review to 1978. Texas Rep Biol Med 1977; 35:1-573.

110. Friedman RM. Interferons and cancer, guest editorial. J Natl Cancer Inst 1978; 60:1191-1194.

111. Yap HY, Buzdar AV, Cabanillas F, et al. Leukocyte interferon-induced tumor regression in human metastatic breast cancer, multiple myeloma and malignant lymphoma. Ann Intern Med 1980; 93:399-406.

112. Schroder EW, Black PH. Retinoids: Tumor preventers or tumor enhancers?, guest editorial. J Natl Cancer Institute 1980; 65:671-674.

113. Haydey RP, Reed ML, Dzubow LM, Shupack JL. Treatment of keratoacanthomas with oral 13-cis-retinoic acid. N Engl J Med 1980; 303:560-562.

114. Meyskens FL Jr, Gilmartin E, Chase E, et al. A broad phase II trial of 13-cis-retinoic acid in advanced cancer. Proc Am Soc Clin Oncol, 1981, p 370.

115. Issell BF. Amsarcrine (M-AMSA). Cancer Treat Rev 1980; 7:73-83.

116. Lawrence HJ, Ries CA, Reynolds RD, et al. M-AMSA: A promising new agent in retractory acute leukemia. Proc Am Assoc Cancer Res 1980; 21:438.

117. Schein PS. Spirogermanium: Initial clinical trials. Presented at the Chemotherapy Foundation Symposium IV. Current optimum strategies for clinical cancer chemotherapy. New York, October 22-24, 1980.

118. Trope C, Gynning I, Johnsson JE, Orbert B. A phase II study of spirogermanium (S-99A, Spiro-32) in advanced ovarian carcinoma. Proc Am Assoc Cancer Res 1980; 21:144.

119. DeJaeger RL. Ellipticinium—A new type of plant alkaloid in clinical use in Europe. Presented at the Chemotherapy Foundation Symposium V: Innovative cancer chemotherapy for tomorrow. New York, November 10-12, 1982.

120. Goldsmith MA, Greenspan EM. Chemotherapy of head and neck cancer. In: Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven, 1982, pp 361-372.

121. Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven, 1982.

122. Muggia FM, Carter SK, Young CW, eds. Anthracycline Antibiotics in Cancer Therapy. Martinus Nijhoff, The Hague, 1982.